Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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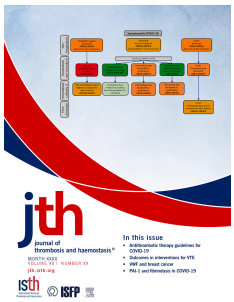

A RANDOMISED CONTROLLED TRIAL TO INVESTIGATE THE USE OF ACUTE CORONARY SYNDROME THERAPY IN PATIENTS HOSPITALISED WITH COVID-19: THE C19-ACS TRIAL

Prapa Kanagaratnam, Darrel P. Francis, Daniel Chamie, Clare Coyle, Alena Marynina, George Katritsis, Patricia Paiva, Matyas Szigeti, Graham Cole, David de Andrade Nunes, James Howard, Rodrigo Esper, Masood Khan, Ranjit More, Guilherme Barreto, Rafael Meneguz-Moreno, Ahran Arnold, Alexandra Nowbar, Amit Kaura, Myril Mariveles, Katherine March, Jaymin Shah, Sukhjinder Nijjer, Gregory YH. Lip, Nicholas Mills, A John Camm, Graham S. Cooke, Simon J. Corbett, Martin J. Llewelyn, Waleed Ghanima, Mark Toshner, Nicholas Peters, Ricardo Petraco, Rasha Al-Lamee, Ana Sousa Marcelino Boshoff, Margarita Durkina, Iqbal Malik, Neil Ruparelia, Victoria Cornelius, Matthew Shun-Shin

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Central Illustration: C19 ACS Trial Main Findings

Hospitalized patients with Covid-19 (n=320)

Acute Coronary Syndrome regimen + Standard care n=160
(3 withdrew before 30 days)

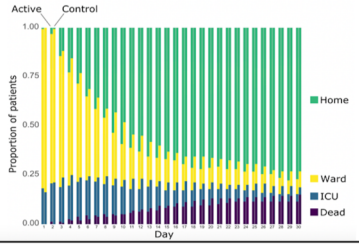
Standard care n=160
(0 withdrew before 30 days)

30 days follow up

All-cause mortality: Adjusted OR 0.71 (95% CI 0.36 to 1.42, p=0.337)

More likely to transition to a better clinical state each day
(OR 1.46, 95% CrI 0.88 to 2.37, Pr(Beta)>0)=93%)

Median time to discharge home was two days shorter
(95% CrI -4 to 0, Pr(Beta)>0=2%)



A RANDOMISED CONTROLLED TRIAL TO INVESTIGATE THE USE OF ACUTE CORONARY SYNDROME THERAPY IN PATIENTS HOSPITALISED WITH COVID-19: THE C19-ACS TRIAL

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Transparency declaration

The lead author affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and registered) have been explained. All authors had full access to the data.

Data sharing statement

The data collected in the study, including anonymised individual patient data and a data dictionary defining each field in the data set, will be made available to others on reasonable request to the corresponding author.

68 **Essentials**

69 • Thrombosis is often found in patients hospitalised with COVID-19, and risk
70 factors for poor prognosis are shared with coronary artery disease.
71 • In a multi-national randomised controlled trial we tested if the addition of
72 standard acute coronary syndrome therapy in 320 hospitalised patients with
73 COVID-19 and cardiovascular risk factors improved clinical outcomes.
74 • No significant reduction in mortality was found with therapy.
75 • There was modest evidence of a reduction in the length of hospital stay
76 without an increase in major bleeding.
77

ABSTRACT

Background: Patients hospitalised with COVID-19 suffer thrombotic complications. Risk factors for poor outcomes are shared with coronary artery disease.

Objectives: To investigate efficacy of an acute coronary syndrome regimen in patients hospitalised with COVID-19 and coronary disease risk factors.

Patients/Methods: A randomised controlled open-label trial across acute hospitals (UK and Brazil) added aspirin, clopidogrel, low-dose rivaroxaban, atorvastatin, and omeprazole to standard care for 28-days. Primary efficacy and safety outcomes were 30-day mortality and bleeding. The key secondary outcome was a daily clinical status (at home, in hospital, on intensive therapy unit admission, death).

Results: 320 patients from 9 centres were randomised. The trial terminated early due to low recruitment. At 30 days there was no significant difference in mortality (intervention: 11.5% vs control: 15%, unadjusted OR 0.73, 95%CI 0.38 to 1.41, p=0.355). Significant bleeds were infrequent and not significantly different between the arms (intervention: 1.9% vs control 1.9%, p>0.999). Using a Bayesian Markov longitudinal ordinal model, it was 93% probable that intervention arm participants were more likely to transition to a better clinical state each day (OR 1.46, 95% CrI 0.88 to 2.37, Pr(Beta>0)=93%; adjusted OR 1.50, 95% CrI 0.91 to 2.45, Pr(Beta>0)=95%) and median time to discharge home was two days shorter (95% CrI -4 to 0, 2% probability that it was worse).

Conclusions: Acute coronary syndrome treatment regimen was associated with a reduction in the length of hospital stay without an excess in major bleeding. A larger trial is needed to evaluate mortality.

Trial registration number: NCT04333407.

INTRODUCTION

Hospitalised patients with COVID-19 respiratory disease often develop thrombotic complications.[1,2] Observational studies have consistently found a history of coronary artery disease and cardiovascular risk factors such as hypertension and diabetes are associated with severe disease and mortality from COVID-19 infection.[3,4] These would be a peculiar findings if COVID-19 were primarily a respiratory disease.

Cardiac biomarkers, such as troponin, are frequently elevated in hospitalised patients with COVID-19, and are associated with poor prognosis.[5-7] Whilst arterial thrombosis in atheromatous coronary vessels might be a potential explanation, these biomarkers do not allow differentiation between ischaemic myocardial damage from myocarditis. However, myocardial infarction has been identified in nearly 20% using late gadolinium enhancement MRI after recovery of patients with severe COVID-19 and a raised troponin.[8,9] Furthermore, immune mediated vascular thrombosis and resultant cardiac injury through direct platelet reprogramming, indirect activation, and the development of antiplatelet, antiphospholipid and antiendothelial cell antibodies have been found in patients with COVID-19 infection.[10] These findings imply that myocardial damage from coronary arterial thrombosis may contribute to the morbidity and mortality of severe COVID-19 disease.

Coronary thrombosis and occlusion results in acute coronary syndromes (ACS). Whilst the mechanism initiating thrombosis may differ in COVID-19 from conventional causes of ACS, it is possible that the shared risk factors results in a shared therapeutic target. Mortality from ACS has been transformed by the benefits of antiplatelet, anticoagulant and statin therapy.[11] We hypothesised that a combination ACS treatment regimen may

have a beneficial impact on patients hospitalised with COVID-19 by preventing myocardial damage. The additive effects of these drugs in ACS were tested incrementally in sequential trials over many years. Replicating such a strategy in COVID-19 would be impractical. We therefore opted for a pragmatic approach of testing an established ACS regimen that could be delivered orally rather than parenterally.[12]

Herein, we report the safety and efficacy findings of a randomised open-label multicentre study of the addition of a conventional acute coronary syndrome regimen (aspirin, clopidogrel, low-dose rivaroxaban, atorvastatin and omeprazole) in patients hospitalised with COVID-19 infection who were either aged >40, or had a history of coronary disease, diabetes or hypertension.

METHODS

Trial design and oversight

C19-ACS was a multi-centre open-label prospective randomised control trial that compared the addition of acute coronary syndrome therapy in patients admitted to hospital for treatment of COVID-19 and at risk of cardiovascular complications to standard care. The study was overseen by the trial steering committee and an independent data and safety monitoring board. The trial was approved by the West London and GTAC Research Ethics Committee (Ref: 20/LO/0574) in the United Kingdom (UK) and the Comissao Nacional de Etica em Pesquisa (Ref: 4.171.639) in Brazil. The study was conducted in accordance with the Good Clinical Practice guidelines. All patients (or appropriate surrogate if capacity lacking) provided informed consent.

The trial was funded by the Coronary Flow Charitable Trust and the Imperial College COVID-19 fund, which had no role in the design, analysis or reporting of trial results.

The members of the writing committee declare that the data are accurate, complete and collected in adherence to the protocol. The trial protocol and statistical analysis plan are appended as Supplementary Materials.

Recruitment

Recruitment started in the UK in April 2020 across 5 sites and then expanded to Brazil on the 24th of September 2020 across 4 sites. The study was terminated in November 2021. C19-ACS enrolled patients aged 18 years and over who were admitted for inpatient hospital treatment for COVID-19 with the presence of cardiovascular risk factors. Infection was confirmed by one or more of; ‘positive test for COVID-19 viral infection (either rapid antigen testing or polymerase chain reaction tests), chest

radiograph or CT suggestive of COVID-19 (based on local radiologist or clinician review), or typical lymphopenia (as per local laboratory reporting)'.

Patients were required to have one or more of the following cardiovascular risk factors: diabetes mellitus, hypertension, known coronary artery disease, and age ≥ 40 years. Exclusion criteria included: clear evidence of an acute coronary syndrome or myo-pericarditis that required specific treatment to preclude randomisation, evidence of active bleeding, pregnancy, and age <18 years. Participants were followed-up for 30 days.

Randomisation

Participants were randomized 1:1 to intervention or control using an in-house, web-based, system with minimisation across four clinical factors (age ≥ 60, presence of diabetes mellitus, presence of coronary artery disease, sex) and random factor (0.2). The intervention arm was Aspirin 75mg once daily (300mg loading dose), Clopidogrel 75mg once daily (300mg loading dose), Rivaroxaban 2.5mg twice daily, Atorvastatin 80mg once daily and Omeprazole 20mg once daily. Modifications of this regimen to account for drug interactions (e.g., statins with macrolide antibiotics), existing or new indication for anticoagulation or need for parenteral routes are described in the Supplementary Appendix. Participants in the control arm continued any of these medications if they were already receiving them or if developed a new indication for one during the study. Standard care in both arms was at the discretion of the admitting team and was not altered by the study team. Therapy was for 28 days, continuing after discharge. Participants could be enrolled into other clinical trials for COVID-19, unless they were testing anti-platelet, anti-coagulant, or statin therapies.

Follow-up and data collection

Participants were followed-up for 30 days. Due to the pandemic, all follow-up was conducted remotely. During their in-patient stay, study teams used hospital records to ascertain adverse events, escalation of care, and discharge details. After 30 days participants (or their preferred contact provided at enrolment) were telephoned to ascertain their status, collect further information on adverse events (such as re-admission to a different hospital), and to ensure that those in the intervention group returned to their pre-existing medications.

Outcomes

The primary efficacy outcome was mortality at 30 days. The primary safety outcome was bleeding (assessed using the Bleeding Academic Research Consortium (BARC)[14]) at 30 days. The key secondary outcome was participants daily clinical status over the 30 days on a 4-point ordinal scale (at Home, in Hospital, on an Intensive Therapy Unit (ITU) or equivalent environment, or Dead), a simplification of the WHO recommended ordinal scale for collecting data in COVID-19 trials.[15] Additional secondary efficacy outcomes included the time to discharge (duration/length of hospital stay). Additional safety outcomes included BARC 3 to 5 bleeds, BARC5 bleeds (bleeds resulting in death), thromboembolic events, and cessation of therapy in the active arm.

Monitoring and adjudication

The trial monitor performed reviewed documentation via videoconference and e-mail to the national and international sites. All deaths, and 25% of the study data were subject to monitoring, and original source documentation reviewed. All deaths, bleeding, and thrombosis events were submitted on digital adverse event forms and reviewed by a central adjudication committee who categorised bleeds according to the BARC classification.

Statistical analysis

The primary analysis was conducted on the intent-to-treat population that included all randomized participants in the arms they were allocated to regardless of subsequent treatment received.

The effect size for the primary efficacy and safety outcomes are presented as odds ratios and their associated 95% confidence intervals (95% CI) and p-values, calculated using logistic regression, including sex, age, recruitment site, presence of diabetes mellitus, coronary artery disease, and hypertension as covariates. Both unadjusted and adjusted results are presented.

The key secondary outcome of a daily ordinal scale was analysed using Bayesian first-order Markov longitudinal ordinal model.[13] This method has been previously described and used in both COVID-19 and other trials.[14,15] The model includes the previous day's state, a flexible function of time since randomization (to allow a non-constant hazard rate), non-proportional odds effect for time (as the mix of events can change over time), and a time by arm interaction (to allow for the effects of therapy to change over time), in addition to the minimisation and stratification covariates above. This model was fitted using an MCMC algorithm and the "rmsb" package in the "R" statistical environment. The model used non-informative normal priors for the beta parameters with a standard deviation of 100, and intercepts with a Dirichlet prior with a concentration parameter of 0.455. Odds ratios, 95% credible intervals (CrI), and probability of the coefficient being >0 are reported. From sample draws of the fitted model, the median time to discharge was calculated.

No correction for multiple testing was made. Missing data were not imputed for any variables used in the analysis. The trial's detailed statistical analysis plan is included in supplementary material.

Sample size

Sample size calculations during a pandemic of a novel disease are challenging. We originally calculated that based on an estimated mortality rate of 25% in patients admitted to hospital with COVID-19[4], approximately 3062 patients would provide 90% power at the 5% significance level to detect a reduction in mortality by 20% with an estimated 2% loss to follow-up. The key secondary outcome of an ordinal scale and longitudinal analysis was made without reference to unblinded data and was based on emerging statistical practices of other trials of therapies in COVID-19, and public recommendations from health authorities (such as the WHO), and extensive work by biostatisticians involved in COVID-19 work. A detailed statistical analysis plan is included in supplementary material.

Protocol changes and early termination

Throughout the trial the Trial Management Group took recommendations from the Trial Steering Committee (TSC) which was advised by the Data Monitoring Committee. Initially the trial was designed with an initial phase based on biochemical markers (including d-dimer and troponin), with a target of 3062. Due to difficulties obtaining regular blood tests during the pandemic, this was dropped; and due to tapering recruitment as we emerged from the first wave of COVID-19 and methodical recommendations from the WHO and other clinical trials we switched to the longitudinal Bayesian ordinal model for the key secondary end-point. Finally, the Trial Steering Committee, based on a recommendation of the Data Monitoring Committee terminated the trial early for futility based on the recruitment and event rate for the primary endpoint (Supplementary Materials). This occurred after 320 patients had been enrolled.

264

RESULTS

Recruitment and follow-up

320 patients were enrolled and randomized, 160 to the intervention, and 160 to the control. One participant, randomized to intervention withdrew from the study immediately after randomisation, and provided no baseline or follow-up data. Two participants, randomized to intervention, withdrew from the study at the time of discharge from hospital and contributed data until this point. All other participants completed the 30-day phone call.

Baseline characteristics

Patients were enrolled from 5 hospitals in the UK (46%) and 4 hospitals in Brazil (54%). The mean age was 64 years, with 99% of participants aged 40 years or over, and 62% of participants were male. Cardiovascular risk factors were common, 60% had a history of hypertension, 39% diabetes, and 21% coronary artery disease. A valid troponin was available at baseline (within 6 days before to 2 days after randomisation) in 82% of participants. Baseline troponin was positive (>=32 ng/L) in 24% of these participants (median 10.8, IQR 5 to 27.9). Other baseline characteristics are shown in Table 1.

Exposure to intervention

As a pragmatic open-label trial of five drugs, participants randomised to intervention may not have received all five drugs. For example, if a patient declined a statin, atorvastatin was not started but other trial drugs were. Conversely, some participants randomized to the control group were already on some of the trial drugs (e.g., due to a history of coronary artery disease). These medications were continued. Of the participants randomised to intervention 91% received aspirin, 92% clopidogrel, 77% rivaroxaban 2.5mg BD, 87% atorvastatin or another statin, and 93% omeprazole or

another PPI. In the participants randomized to control 31% received aspirin, 13% clopidogrel, 0% rivaroxaban 2.5mg BD, 53% atorvastatin or another statin, and 62% omeprazole or another PPI. Overall, 58% (93/159) of the intervention group and 0% (0/160) of the control group received at some point one of all 5 therapy classes: any two anti-platelets, rivaroxaban 2.5mg twice daily, any statin, and any PPI. Further details are shown in Table 2.

Primary outcome

At 30 days, 18/157 (11.5%) of participants in the intervention group, and 24/160 (15.0%) in the control group had died. There was no significant difference between the groups (unadjusted OR 0.73, 95%CI 0.38 to 1.41, p=0.355; adjusted OR 0.71, 95%CI 0.36 to 1.42, p=0.337). Bayesian analyses are reported in the Supplementary Appendix.

Secondary outcomes

The daily clinical state (at home, in hospital, on ITU, dead) over 30 days was tabulated, with the proportion in each category shown in Figure 2. Using a Bayesian Markov longitudinal ordinal model, it is 93% probable that participants randomized to the intervention are more likely, as compared to control, to transition to a better clinical state each day (OR 1.46, 95% CrI 0.88 to 2.37, Pr(Beta>0)=93%; adjusted OR 1.50, 95% CrI 0.91 to 2.45, Pr(Beta>0)=95%). The median time to discharge home was two days shorter in the intervention group (95% CrI -4 to 0), with only a 2% probability that it was worse.

Safety

There was no significant different in bleeding (across BARC grades) between intervention and control (13/159 8.2% vs 9/160 5.6%, p=0.5). Major bleeds (those adjudicated BARC3 or above) were infrequent, and not significantly different

between the arms (intervention 3/159 (1.9%); control 4/160 (2.5%); difference 0.6%, 95% CI -4.4 to 3.2%, p>0.999). There was one fatal bleed in each arm. All bleeding events and associated BARC classification are detailed in Table 3.

The central coordinating centre was specifically informed about cessation of therapy in 8 participants in the intervention group; two due to bleeding, one due to thrombosis, one due to clinical deterioration, three as patient withdrew consent for the intervention, and one at discharge for unspecified reasons. As a pragmatic trial, therapy could be started or stopped by both participants and their physicians during the 28 days so true discontinuation rates may be higher than this.

DISCUSSION

C19-ACS is the first study to test an acute coronary syndrome treatment regimen in patients hospitalised with COVID-19 and a risk factor for coronary disease. The trial was terminated early and found no significant evidence that the therapy reduced mortality. However, there was moderate evidence that patients were more likely to improve each day and have a shorter hospital stay. Overall, bleeding was uncommon and, whilst the study had limited power to detect a difference, was similar between the arms.

This study enrolled a broad group of patients with COVID-19 with easily identified risk factors to a well-established therapy that may overlap in pathology.

Since the initiation of this trial, multiple randomised trials testing the individual components of the ACS therapeutic regimen in patients with COVID-19 have reported.

Anti-platelet *mono*-therapy has not been found to be effective in reducing mortality across a wide range of patient groups from the critically unwell (REMAP-CAP)[16], those hospitalised (RECOVERY)[17],and those in the community (ACT)[18]. However, and consistent with RECOVERY this study found modest evidence that therapy reduced the median length of stay by 1 day. Whilst major bleeding events were low, there was a significant difference between the arms in RECOVERY (1.6% vs 1%).[17]

There has however been modest evidence that therapeutic anticoagulation with low molecular weight or intravenous heparin reduces the need for organ support in

hospitalized, but not critically unwell patients (ATTACC/ACTIV-4a/REMAP-CAP).[12] However, the INSPIRATION study found no benefit to intermediate-dose anticoagulation over prophylactic dose but this regimen did not include antiplatelet agents and only recruited patients requiring ICU treatment.[19] Limited benefits in some end-points were found in a trial of rivaroxaban in hospitalized patients (MICHELLE).[20]

The INSPIRATION-S study, recruiting "critically ill" patients with COVID-19 did not find benefit with atorvastatin, and nor did the RESIST trial in those only hospitalized.[21,22]

The results of C19-ACS are broadly compatible with the findings of these trials, with modest evidence that it increased the probability of clinical improvement and reduced hospital stay. The RECOVERY trials show us that the efficacy of therapy can be dependent on patient's clinical status.[23] For dexamethasone, little efficacy was found in in those with the mildest disease. Conversely, there is a possibility that there comes a point where the clinical state has deteriorated so that no therapy could work. This trial recruited in-hospital patients receiving ward-level care, and they may have been towards the milder end of the spectrum. Nevertheless, a fifth of patients were within ITU within 1 day of recruitment. Many of these trials recruiting critically unwell patients were neutral.

Unusually for an infectious disease, the risk factors for severe COVID-19 disease mirror those of coronary disease. Furthermore, there is a nearly four-fold increase in mortality in patients with coronary disease[24], and imaging of survivors of severe disease show around 20% have suffered myocardial infarction.[8] Many patients with coronary artery disease are undiagnosed,[19] underling the importance of enrolling of

those with risk factors, as occurred with the pragmatic recruitment strategy for C19-ACS. This regimen is known to be an effective treatment for ACS[11], so the finding of clinical improvement and low and similar rates of bleeding shows promise.

There is evidence that the coagulopathy in COVID-19 illness is distinct from other critical illnesses, As compared to other causes of sepsis, higher fibrinogen and D-dimer levels and only minor changes in platelet count are seen with COVID-19.[25] However, the differences are not limited to the coagulation pathway, and also include direct endothelial cell dysfunction (perhaps via the ACE-2 receptor) and pulmonary vascular constriction (particularly in the setting of hypoxia).[26-28] Furthermore, pulmonary thrombosis is likely to be important, with autopsy studies showing almost ten times the rate of pulmonary thrombus in COVID-19 compared to influenza.[29]

The benefit of the C19-ACS regimen may therefore reflect a systemic prothrombotic illness in which both antiplatelet-responsive atherosclerotic and anti-coagulant-responsive thrombosis are therapeutic targets. Multiple mechanisms of cardiac injury occur in COVID-19 and it is possible that the broader range of interventions seen in the ACS bundle treats a larger spectrum of potential insults which may be occurring in the same patient. Our data provide the impetus for further investigations of anti-thrombotic therapies in patients with COVID-19 infection.

Limitations

This trial was underpowered for the primary outcome of mortality as due to inadequate recruitment rate it was terminated early.

We were aware of a bias against recruiting to the study due to safety concerns about bleeding. This may have resulted in selecting a patient population with a lower risk of bleeding. The incidence of major bleeding was low, and similar to the 1% seen in the RECOVERY-aspirin trial. However, as a pragmatic trial, not all participants received all the trial medications due to individual contra-indications. Due to the nature of the pandemic, data for exposure to trial medications was based on issued prescriptions and participant phone calls rather than pill counts. Not all patients would have completely adhered to the trial medications throughout the 28-days. These two factors will reduce the reported incidence of bleeding.

Furthermore, the study was underpowered to detect small absolute differences in the incidence of major bleeding and the common use of prophylactic heparin in medical inpatients in the control arm and the continuation of existing anti-platelet and anti-coagulant therapy may have reduced any differences between the arms resulting from the therapy.

We aimed to enrol a broad range of patients with minimal exclusion criteria. Enrolling patients based on biomarkers, such as D-dimer may have selected patients in which therapy was more likely to be successful. However, other trials, enrolling with such as strategy for anti-coagulation have had variable results. The RAPID trial of therapeutic-dose heparin finding a reduction in mortality, though this was a small study and a secondary end-point.[30] Conversely the ACTION trial found no benefit of higher dose Rivaroxaban (15 to 20mg) despite enrolling those with raised d-dimer.[31]

As with many other trials repurposing existing therapies for COVID-19, this trial was open label. This may have introduced bias. However, it might be expected to act in the converse direction, with the addition of therapies requiring a longer stay to assess tolerability and with the participant's responsible clinicians more likely to report bleeds if they are known to be on additional anti-platelet or anti-coagulant therapy.

CONCLUSION

The C19-ACS trial was underpowered to determine whether an acute coronary syndrome treatment regimen improved survival in patients hospitalised for COVID-19 with risk factors for coronary disease. However, there was moderate evidence that it accelerated clinical improvement and reduced the median length of hospital stay. This merits further evaluation in a larger trial.

Author Contributions

PK was chief investigator for C19-ACS.

DF, PK, CC, AM, MSS formed the C19-ACS Committee.

MSS, MS, VC formed the Statistical Analysis Protocol working group.

The trial steering committee comprised of GL, PK, JC, MT, WG, GC, VC, AB, AM, DF, MSS, MS, GC, RAL, CC.

The DMC was formed by NM, ML, SC.

Principal investigators at UK sites were MK, RM, JS, SN, NR.

Principal investigators at Brazil sites were DC, PP, DAN, RE, GB, RMM.

Patient recruitment was overseen by AM, CC, GK, MM, KM, PP.

The imperial clinical trials unit provided support via AM, MD.

The manuscript was prepared by PK, CC, MSS with contributions from all authors.

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Conflict of Interest

Nothing to declare: DF, DC, AM, GK, PP, MS, GC, DAN, JH, RBE, MK, RM, GB, RAM, AK, MM, KM, JS, SC, MJL, NSP, RP, ASMB, MD, IM, NP, VC,

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475 reports fees for participation in Advisory board from Amgen, Novartis, Pfizer,
476 Principia Biopharma Inc- a Sanofi Company, Sanofi, SOBI, Grifols, UCB, Argenx,
477 Cellphire, Hutchmed. Lecture honoraria from Amgen, Novartis, Pfizer, Bristol Myers
478 Squibb, SOBI, Grifols, Sanofi. Research grants from Bayer, and BMS/Pfizer. MT
479 reports: MorphogenIX: Scientific Advisory Board personal fees, J&J/Actelion:
480 Personal fees/honoraria. RAL receives speaker's honoraria from Philips Volcano,
481 Medtronic & Menarini. MSS has received honoraria from Pfizer (<£500).
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590 **TABLES**

591 Table 1: Baseline characteristics

	Intervention N=159	Control N=160	All N=319
Recruitment country			
UK	73 (46%)	73 (46%)	146 (46%)
Brazil	86 (54%)	87 (54%)	173 (54%)
Inclusion risk factors			
Age >= 40	158 (99%)	159 (99%)	317 (99%)
Diabetes	62 (39%)	61 (38%)	123 (39%)
Hypertension	97 (61%)	95 (59%)	192 (60%)
Coronary artery disease	28 (18%)	39 (24%)	67 (21%)
Demographics			
Age, mean ± sd	63.9 ± 11.6	63.3 ± 11.9	63.6 ± 11.7
Median (IQR)	65 (IQR 55 to 72)	63.5 (IQR 55 to 73)	64 (IQR 55 to 73)
Male	97 (61%)	101 (63%)	198 (62%)
Female	62 (39%)	59 (37%)	121 (38%)
Angina	9 (6%)	11 (7%)	20 (6.3%)
Myocardial infarction	19 (12%)	26 (16%)	45 (14.1%)
Percutaneous coronary intervention	16 (10%)	17 (11%)	33 (10.3%)
Coronary artery bypass graft	10 (6%)	12 (8%)	22 (6.9%)
Asthma	14 (9%)	11 (7%)	25 (7.8%)
Active cancer	5 (3%)	5 (3%)	10 (3.1%)
Current smoker	4 (3%)	3 (2%)	7 (2.2%)
Ex-smoker	37 (23%)	42 (26%)	79 (25%)
Never smoked	55 (35%)	54 (34%)	109 (34%)
Unknown	63 (40%)	61 (38%)	124 (39%)
Troponin (Baseline)			
Value available	130 (82%)	131 (82%)	261 (82%)
Median	10	11	10.8
IQR	(5 to 21.8)	(5 to 33.0)	(5 to 27.9)
Positive (>=32)	29/130 (22%)	33/132 (25%)	62/261 (24%)

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Table 2: Trial medication exposure.

Exposure to the trial medications (or associated classes) at any point during the 28 days of the trial. Rx: Dosage to achieve therapeutic anticoagulation.

	Intervention (n=159)	Control (n=160)
Aspirin	145 (91%)	49 (31%)
Clopidogrel	147 (92%)	21 (13%)
Other anti-platelet	1 (1%)	0 (0%)
Number of anti-platelets		
None	7 (4%)	103 (64%)
One anti-platelet agent	11 (7%)	44 (28%)
Two antiplatelet agents	141 (89%)	13 (8%)
Any anti-coagulant	147 (92%)	116 (73%)
First anticoagulant received		
Rivaroxaban Trial Dose (2.5mg BD)	108 (68%)	0 (0%)
UFH 5,000 Units	1 (1%)	5 (3%)
LMWH Prophylaxis	10 (6%)	45 (28%)
LMWH as part of a local Covid Protocol	4 (3%)	15 (9%)
LMWH Rx	7 (4%)	22 (14%)
Warfarin Rx	3 (2%)	11 (7%)
Apixaban Rx	2 (1%)	9 (6%)
Rivaroxaban Rx	11 (7%)	7 (4%)
LMWH Unspecified	1 (1%)	2 (1%)
Rivaroxaban Trial Dose (2.5mg BD) at any time	123 (77%)	0 (0%)
Any Statin	138 (87%)	86 (53%)
Any PPI	148 (93%)	99 (62%)
Any two anti-platelets, Rivaroxaban Trial (2.5mg BD), any statin, any PPI	93 (58%)	0 (0%)

599 Table 3. Bleeding endpoints

Bleeding Academic Research Consortium (BARC) Bleeding level	Intervention N=159	Control N=160
5 (Fatal)	1 (0.6%)	1 (0.6%)
4 (CABG related)	0 (0%)	0 (0%)
3 (Overt with Hb drop)	2 (1.3%)	3 (1.9%)
3B (Hb drop >=5)	1	2
3A (Hb drop 3 to 5 g/dL)	1	1
1 (not actionable) or 2 (overt, actionable)	10 (6.3%)	5 (3.1%)

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602 **FIGURES**

603 Figure 1: Consort Diagram

604 Figure 2: The proportion of participants in each of the four clinical states, split by the
605 active and control arms (pairs of columns; active left, control right), over the 30 days
606 after randomization.
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